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(54) Title: AN INJECTABLE BONE MINERAL SUBSTITUTE MATERIAL

(57) Abstract: An injectable bone mineral substitute material composition comprises an inorganic bone cement powder and a biologically compatible oil. The oil is an intermixture with the cement powder at a concentration of less than 10 wt% of the total weight of the composition in order to improve the rheology of the same. In a method of intermixing a powder of an implant material and a biologically compatible oil to a composition the oil is mixed with the powder of implant material at an elevated temperature.

AN INJECTABLE BONE MINERAL SUBSTITUTE MATERIAL

Technical field

The present invention relates to a bone mineral substitute material composition. More precisely, the invention relates to an injectable bone mineral substitute material composition comprising an inorganic bone cement powder and a biologically compatible oil. The invention also relates to a method of intermixing a powder of an implant material and a biologically compatible oil to a composition.

Background art

During the last decade, the number of fractures related to osteoporosis, i.e. reduced bone mass and changes in microstructure leading to an increased risk of fractures, has almost doubled. Due to the continuously increasing average life time it is estimated that by 2020 people over 60 years of age will represent 25 % of Europe's population and that 40 % of all women over 50 years of age will suffer from an osteoporotic fracture.

Research for suitable materials to repair or replace bone segments of the musculoskeletal system has been conducted for more than a century. Graft surgery by means of autogenous bone, i.e. bone derived from another site of the body, is one of the methods used for filling a bone cavity, replace bone lost during tumor removal, etc. Autografts are clearly osteogenic, but there is a limited supply of bone. Also, the need of a second surgical site to harvest the graft subjects the patient to additional trauma. To avoid the extra trauma, allografts, i.e. a graft of bone between individuals of the same species but of disparate genotype can be used instead of autografts. Allografts, however, demonstrate a lower osteogenic capacity and new bone formation may occur at a slower rate. This type of graft also exhibits a higher resorbtion rate, a larger immunogenic response, and less revascularisation.

Another problem with allografts is that they may transfer viruses, e.g. hepatitis and HIV virus. Therefore, careful microbiological controls are necessary before transplantation can be performed.

With the aim to reduce or eliminate the need for bone grafting, research has been made to find a suitable artificial bone mineral substitute. There are, however, substantial requirements on such materials. First of all it should be possible to use them in bone defects and they should be resorbed and/or fully integrated within the bone over time. If a tumor is removed from the bone, it should be possible to inject the material and fill the cavity in the bone. Said bone minerals substitute should also be possible to use for additional fixation of osteoporotic fractures. Additionally, it should be possible to inject the material and at the same time, if necessary, contribute in fixation of the fracture. It is not essential for the bone mineral substitute material to be strong enough to stabilize the fracture. The material should, however, be strong enough to significantly decrease the time in which an external cast or brace is necessary by aiding the stability and fracture alignment. If this is possible, the patient's mobility is not limited to the same extent as would be the case if a cast was necessary for a long period of time. This results in decreased risks for stiffness, reduced mobility, and morbidity after operation and also in a reduction of the costs for society.

Therefore, ideally, a hardened bone mineral substitute material should exhibit osteoinduction, i.e. the substitute should recruit mesenchymal cells located near the implant and from revascularisation, the cells being differentiated into bone producing cells. Furthermore, the hardened material should also exhibit osteoconduction, i.e. the substitute should act as trellis for new bone formation.

The mechanical properties of the bone mineral substitute should be as close to cancellous, i.e. spongeous, bone as possible without being brittle but does not have to be strong enough to be possible to use for full weight bearing without added support.

The substitute should also be biocompatible, i.e. accepted by the tissues with little or untoward reaction. It should be non-allergic, non-toxic and non-carcinogenic. Furthermore, the substitute should preferably be at least partly biodegradable starting postoperative but with a certain strength for 1-6 months, in some instances totally replaced by new bone in 1-2 years.

Presently, at least the following bone mineral substitutes are used for the healing or stabilizing of bone defects and bone fractures, namely calcium sulfates, as for instance calcium sulfate hemihydrate, also known as Plaster of Paris, calcium phosphates, as for instance hydroxylapatite, and polymers, as for instance polymethylmetacrylate (PMMA).

In WO 00/45867 a hydraulic cement composition for implantation in the human or animal body is shown, which comprises a calcium source, water and a hydrophobic liquid. The hydrophobic liquid is used in amounts between 10 and 90 wt%, preferably between 30 and 60 wt%, and is able to form an emulsion with the calcium source and water. The purpose of the hydrophobic liquid in the composition is to increase the viscosity of the composition and obtain an open macroporous calcium phoshpate matrix after hardening. Components of the composition are mixed to an emulsion of the hydrophobic liquid. However, such an emulsion can not be used if a large surface area of cement particles are to be coated with a small amount of hydrophobic liquid.

Recently, in PCT/SE99/02475, an improved injectable bone mineral substitute material for filling defects in osteoporotic bone and for additional fracture fixation in

preferably cancellous bone has been developed, which comprises calcium sulfate hemihydrate, hydroxylapatite and an accelerator. Due to the addition of an accelerator the setting time period could be controlled and considerably shortened while the injectable time was still long enough to make it possible to inject the material into e.g. a bone cavity.

These kinds of substitute materials are composed of a powder component and a liquid component which are mixed at the time of surgery, thereby initiating a setting reaction. While in a fluid or semi-fluid pre-cured form, the material is injected directly into the void in the bone or at the fracture site. During the subsequent setting reaction, the material should not reach a temperature (≥44°C) which may cause damage to the surrounding tissue. The hardened paste provides a support by mechanically interlocking pieces of broken bone as well as conforming to the contours of the gap and supporting the cancellous bone. After curing the strength should be at least equal to that of spongeous bone.

It generally takes bone fractures, particularly non-healed fractures, many weeks and months to heal completely. During this period several physical and biochemical factors influence the natural healing process. For example, a variety of genetically driven biochemical events, particularly changes in ion transport, protein synthesis and the like are involved in the repair of fractured bones. The amount of free radicals are increased, especially in inflammatory tissue in fracture repair. The callus formation starts with mesenchymal cells which are transformed into cartilage cells and increase the stability to bone.

Also the proton concentration and superoxide radicals influence the bone formation and bone regeneration. Superoxide radicals and other highly reactive oxygen species are produced in every respiring cell as by-products of oxida-

tive metabolism, and have been shown to cause extensive damage to a wide variety of macromolecules and cellular components. Such an oxidative stress can arise from a surplus in the amount of activated oxygen or from a reduced amount of those molecules which are able to trap the energy of these radicals, so called scavengers. The inability of the cells to remove these free radical species will result in the destruction of biomolecules and cell structures, by means of for example lipid peroxidation, and eventually cell death. Systemically given antioxidants have in animal models been shown to improve fracture healing.

In DE 197 13 229 A1 a calcium phosphate-based bone cement is described. The injectable and hardenable bone cement paste is based on bioresorbable hydroxylapatite-like calcium phosphate containing compounds which, however, contain a cationic antibiotic as an active agent. After hardening the antibiotic is released in biologically active concentrations over a long period for the treatment and prophylaxis of osteomyelitis and ostitis, especially in connection with bone defects and fractures. This is also a well-known treatment.

During the preparation of a bone mineral substitute material it is often difficult to mix the substances in such a way that the mixture can be delivered into a patient within a reasonable period of time during surgery in an operation room. For example, when the powder component of a calcium sulphate or a calcium phosphate based cement is mixed with water, this takes place in a container, from which the mixture is delivered to the treatment site via a nozzle, the material being injected under pressure. During the injection the nozzle may become clogged. The situation is aggravated if for example a fracture is to be treated through a small hole in the trochanter region and the cement has to be injected 10 cm from the injection site, a pressure being built up. Thus, the bone mineral substitute

material must be prepared in a way so that it can be easily injected and the mixing of the cement has to be made rapidly, reproducibly and with a sufficient homogeneity. Such a ceramic material should harden within 6-12 min, preferably between 5-10 min, and the viscosity of the material should be adapted to be easily injected within 5 min. In this connection it is important to prevent crack formations or defects in the hardened cement, which may be caused by insufficient packaging of the bone substitute material after injection.

The viscosity of the material should be adapted in order to be easy to inject into the bone for 1-5 minutes after start of mixing procedure. In this connection problems are often obtained when the bone cement material is injected if not handled with extreme caution. This is especially true if the cement has to be injected through a long nozzle with a small diameter. Thus, it is also important to eliminate the drawback of high viscosity at delivery by improving the rheology of the bone mineral substitute material.

There is also a demand for a bone mineral substitute material which prevents negative effects during the bone regeneration process, such as minimize the risk of infections and other complications, and improves and accelerates the tissue and bone healing at the treatment site.

Furthermore, when joint implants, e.g. hip and knee joint implants, are fixated in the bone by means of what is called a cementless fixation, it is very important that the shape of the bone cavity, into which the implant is to be placed, exactly matches the shape of the implant. In practice, the bone cavity preparation always gives rise to a mismatch to a greater or less extent between the bone cavity and the implant. This mismatch results in a reduction in stability and a decreased probability of a successful bone ingrowth and ongrowth onto the implant

surface. The degree of bone ingrowth/ongrowth is in turn extremely critical for the long term fixation and thereby the survival of the implant.

Summary of the invention

The purpose of the invention is to provide a composition comprising a bone mineral substitute material, in which the above-mentioned drawbacks have been reduced or eliminated.

In order to achieve this purpose the bone mineral substitute material composition according to the invention has the characterizing features of claim 1.

The inventive composition has an improved rheology in comparison with other compositions according to the state of the art without reducing the mechanical strength of the ceramic materials. Bone cements prepared from the inventive composition can readily be manufactured at low costs and have both rapid and long-lasting pharmacological effects which improve the healing capacity. It could also be used in subcutaneous applications for controlled slow release of pharmaceutical drugs as for example in chronic conditions, such as osteoporosis, rheumatoid arthritis, diabetes, asthma, etc.

In order to explain the invention in more detail reference is made to the accompanying drawings in which

FIG 1 shows the differences in injection time with a bone mineral substitute material composition according to the invention and a control cement;

FIG 2 shows the setting times obtained with the corresponding cements; and

FIG 3 shows the compressive strength obtained with the corresponding cements.

By using a bone mineral substitute prepared from the injectable composition according to the invention as a reservoir for a biologically active substance several positive effects are obtained which will enhance the tissue

regeneration. Bone ingrowth, bone ongrowth, as well as fracture healing is speeded up and inflammation is reduced if for example an antioxidant is included in the cement.

Biological effects are also obtained in the bone regeneration process if antibiotics and corticoids are used as the active substance to be released over a period of time. Other useful substances which influence the bone formation and bone regeneration are primarily hormones (calcitonin, insulin, glucocortocoid, PTH) and growth factors of the protein type (bone morphogenic protein, osteoquinine, osteonectine, insulin like growth factors). These substances are used alone or in combination with other substances such as cytostatics, bisphosphonates, and growth hormones in order to increase wound healing capacity of the bone cement. One preferred hormone to be used in the cement is oxytocin.

The biologically active substance should comprise 0.05-10 wt% of the final bone mineral substitute, preferably 0.1-5 wt%. By gradually leaking out high concentration are obtained locally and the concentration of the active substance is focused on certain sites. The release of the active substance takes place during a period of approximately six weeks, the maximum release occurring during the first week.

In order to speed up the fracture healing and exert a positive effect on the fracture haemathoma, the biologically active substance is an antioxidant. Preferably, the antioxidant is a vitamin E, most preferably α-tocopherol, but other vitamins can also be used to exert positive effects on fracture healing.

A systemic antioxidant treatment reduces the number of free radicals locally at the fracture site. With vitamin E as antioxidant neither any systemic negative effect nor any toxic reaction is obtained. For the inventive composition, 50 g of composition including 10 wt%

vitamin E corresponds to a concentration of 0.007 wt% of the body mass in a human (70 kg). Even if the concentration in the material would be several times higher, it would not cause any problem since vitamin E is slowly released from the material in the body.

With this in view a non-invasive radiographic contrast medium can also be included in the inventive composition in order to increase the radiopacity.

According to the invention, the biologically active substance can be dissolved, suspended or emulsified in a biologically compatible oil. In this connection an oil means a substance or a mixture of substances, which is an unctuous viscous liquid or solid easily liquefiable on warming and is not miscible with water, and which can be of animal, vegetable, mineral, or synthetic origin. Mineral oils or lipids, oils or fats from terrestrial and marine animals as well as plants can be used as long as they are pharmacologically inert and has no interaction with the pharmaceutical active ingredient(s) used in the inventive bone mineral substitute. These oils can be used in raw or purified form.

Representatives of mineral oils are a silicone oil from Dow Corning Corp. (Dow 200 Fluid, $3.5*10^{-4}$ m^2/s, 350 cSt) and a mineral oil Seppic with the designation ISA 724.

Preferably, the oils used are from oil seeds, such as colza seed, cotton seed, croton seed, illipe seed, kapok seed, linseed, and sunflower. Other suitable oils from plants are cocoa oil, rice oil, rape oil, olive oil, soy-bean oil, maize oil, colza oil, almond oil, peanut oil, palm oil, and coconut oil. Examples of animal oils are castor oil, lard oil, whale oil, fish oils, and bone oil. An oil can be used alone or in combination with one or more other oils.

Fats are exemplified below, which can be used in the inventive bone mineral substitute material composition,

their melting points being given within parenthesis. Hydrogenated castor oil (79-88°C), hydrogenated beef tallow(38-62°C), hydrogenated lard oil(38-62°), cacao butter(45-50°C), fatty acid glycerol esters such as glycerol monolaurate (44-63°C), glycerol monomyristate (56-70.5°C), glycerol monopalmitate (66,5-77°C), glycerol monostearate (74.5°C), glycerol dilaurate (39-54°C), glycerol dimyristate (54-63°C), glycerol dipalmitate (50-72.5°C), glycerol distearate (71-77°C), glycerol distearaet (71-77°C), glycerol trimyristate (44-55.5°C), glycerol tripalmitate (55,5-65,5°C), glycerol tristearate (64-73.1°C), wax materials such as beeswax (60-67°C), carnauba wax (80-86°C), Japan wax (50-54°C) and spermaceti (42-54°C), hydrocarbons such as paraffin (50-75°C), micro-crystalline wax (74-91°C), fatty alcohols such as cetyl alcohol (47-53°C), stearyl alcohol (56-62°C) as well as higher fatty acids such as lauric acid (42-42.2°C), myristic acid (53.4-53.6°C), palmitic acid (63.8-64,0°C), stearic acid (70.7°C), behenic acid (86-86.3°C) and arachidic acid (77.5-77.7°C).

The biologically active substance is mixed in the inventive bone mineral substitute material composition by being dissolved, dispersed or emulsified in the biologically compatible oil. If the substance is of hydrophobic nature it can be dissolved in the oil. If hydrophilic, it is preferably dispersed or suspended as a fine powder in the oil. It is only when the biologically active substance in itself is a liquid that it has to be emulsified in the oil.

By including a biologically compatible oil in the injectable bone mineral substitute material composition according to the invention crack formation and the formation of pores in the hardened bone mineral substitute is reduced, as well as the degradation of a easily water soluble ceramic. Furthermore, the strength of the resulting

hardened material is very little affected. In order to achieve these effects, the concentration of the oil should be more than 1 wt% but less than 10 wt% of the total weight of the composition in order to improve the rheology of the same. Preferably, the concentration of oil should be between 2 and 6 wt% of the total weight of the composition.

In order to achieve a composition according to the invention, a powder of an implant material must first be mixed with the oil. This can with advantage be performed in a rolling bottle. Suitable powdered implant materials comprise powdered bone substitute materials of the mineral type, such as for example hydroxylapatite, as well as powdered polymers, which are used in endoprosthetic joint replacements.

However, it is important that the mixing of the powdered implant material and oil takes place at an elevated temperature, i.e. between 30 °C and 120 °C, preferably between 50 °C and 90 °C, for example in an oven. Preferably, the mixing is performed at 80 °C for 24 hours.

While not wishing to be bound by any particular theory or mode of operation, it appears that the oil forms a thin film around some or all the powder particles of implant material.

The mixture of implant material and oil, which still has the properties of a powder, can then be mixed at ambient temperature with remaining ingredients to composition. When a calcium sulphate/hydroxylapatite cement is prepared, such remaining ingredients comprise water and seeds of calcium sulphate dihydrate, which then comprise an injectable composition in the form of a paste.

Since vitamin E is an oily substance it can be used in the bone mineral substitute material composition as the active substance and as the biologically compatible oil at the same time.

With reference to FIG 1, a bone mineral substitute material composition according to the invention comprising vitamin E was compared in a compression test equipment with a cement devoid of a biologically compatible oil. Both cements consisted of a powder of 40 wt% hydroxylapatite, 0.4 wt% accelerator (particulate calcium sulphate dihydrate), and 59.6 wt% calcium sulfate hemihydrate, which was mixed with water at a liquid/powder (L/P) ratio of 0.25 ml/g. In the inventive bone mineral substitute material composition, 1 wt% vitamin E was added to the powder (a).

The machine was coupled to syringe (19 mm diameter) filled with treated and untreated cement, respectively, the load versus time after the start of mixing (time of injection) being measured when the syringe was emptied at a rate of 10 mm/min. Four comparative tests were performed which represent the curves obtained with (a) and without (b) vitamin E, respectively.

As seen in FIG 1, it is considerably easier to inject a cement with vitamin E than without the same. The load at a certain time is considerably lower. For example, at a time of injection of about 3 min the difference in load was as large as 100 N.

No significant difference in setting time (FIG 2) or compressive strength (FIG 3) as defined according to standard methods has been obtained between control cements and the inventive cement containing vitamin E as the biologically active substance. In FIG 2, a' and a represent the initial and final setting time, respectively, for a bone mineral substitute material composition with 1 wt% vitamin E. The bars denoted with b' and b show the corresponding setting times for the same bone mineral substitute material composition without vitamin E. In FIG 3, a and b represent the compressive strengths obtained with a bone

mineral substitute material composition with (a) and without (b) 1 wt% vitamin E, respectively.

The preferred major kinds of cements to be used in the bone mineral substitute materials according to the invention are composed of calcium sulphates and/or calcium phosphates. Examples of different types of inorganic cements to be used in the inventive composition are amorphous calcium phosphate I (ACP), amorphous calcium phosphate II (ACP), monocalcium phosphate monohydrate (MCPM; $Ca(H_2PO_4)_2 \cdot H_2O$), dicalcium phosphate dihydrate DCPD (brushite; $CaHPO_4 \cdot 2H_2O$), octacalcium phosphate ($Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$), calcium deficient hydoxylapatite (CDHA; $Ca_9(HPO_4)(PO_4)_5(OH)$), tricalcium phosphate (TCP; $Ca_3(PO_4)_2$), and hydoxylapatite (HA; $Ca_{10}(PO_4)_6(OH)_2$).

Preferably, a mixture of calcium sulfate hemihydrate, calcium phosphate, and an accelerator is used. The most preferred bone mineral substitute cements are hydroxylapatite and calcium sulfate hemihydrate.

The accelerator comprises reacted calcium sulfate dihydrate present in an amount of about 0.1 to about 10 wt% of the bone mineral substitute material composition, preferably about 0.1 to about 2 wt%. The accelerator should have a particle size of less than 1 mm.

Preferably, the calcium phosphate has a Ca/P-ratio between 0.5 and 2. Likewise, it is preferred that the particulate calcium phosphate is hydroxylapatite (HA), tricalcium-phosphate (TCP), or a mixture thereof. The particulate calcium phosphate would preferably have a particle size of less than 20 μm, preferably less than 10 μm, but in certain indications larger sizes could be used up to 10 mm.

A powder of the ceramic can for example be made in a turbo mixer at high velocity. The particulate calcium phosphate in the dry powder should comprise between 20 and 80 wt% of the total weight of the powder, preferably

between 30 and 60 wt%. The powder is sterilized by means of radiation or gas (ethylene oxide, ETO).

Then the powder component is either packed in for example a paper bag or prepacked in a mixing polymer container. The packaging (paper bag or mixing container) is sterilized by means of gas or irradiation, preferably by means of gamma-irradiation.

When producing the injectable bone mineral substitute material composition, the biologically compatible oil containing the active substance dissolved, suspended or emulsified therein may be added to and mixed with either the powder component or the liquid component, the setting reaction being initiated. This can be done by for instance ultrasound dispersion, vibration, etc. The oil can also be prepacked in a separate container in order to be mixed with the other components at the time of use. In this connection care is taken in order to adjust the total water content with respect to the final substitute.

For example, vitamin E can easily be prepared as a stable emulsion in distilled water. The emulsion is then packed or sterile filled in for example a plastic bag which preferably is protected from light by an aluminium envelope, in an aluminium containing polymer foil or in a glass ampoule.

An efficient mixing system must be available in order to prepare the bone mineral substitute material composition according to the invention. The mixing can take place in a conventional cement mixing system. However, the mixing container is preferably of that type which can suck the aqueous component into the powder component (German Patent 4409610). This Prepack™ system is a closed mixing system in combination with prepacked components in a flexible foil bag. Other mixing devices can of course also be used, for example two interconnected soft bags which can be adapted to a delivering cylinder. It is not necessary to perform

the mixing in vacuum since no toxic substances are involved in the inventive composition.

The mixing of the composition is according to the invention performed under conditions of subatmospheric pressure, e.g. vacuum. However, an atmospheric pressure can also be used. Preferably, the powder component of the composition is sterilized by means of radiation before it is mixed with the sterile liquid component.

If a hip fracture is going to be treated a nozzle having a diameter of 6-8 mm is used when a cement paste is injected, and when treating a tumour a diameter of 10 mm is suitable. However, if a small bone defect is to be treated or if the injection is performed at a considerable distance from the injection site, the composition must be injected through a small syringe or nozzle. This can surprisingly be performed by means of injecting the bone mineral substitute material composition according to the invention due to the reduced viscosity of the composition. Thus, a nozzle having a diameter between 1 mm and 10 mm can be used.

The inventive composition is preferably used for preparing a bone mineral substitute, as an implant containing an active pharmaceutical drug which encases the active substance(s) for subsequent release to the body. The composition can also be used for manufacturing pre-set cements for local applications at other sites within the body in order to perform sustained drug release there. These pre-set cements can have the configuration of square blocks, pellets, rods, and small circular beads having a diameter from about 10 mm to about 3 mm in order to increase the surface area. In this case the active substance is used for improving the tissue characteristics and the tissue response.

The different configurations of pre-set cements can also be threaded on a string of a non-resorbable or a resorbable material, e.g. polylactide or polyglycol. These

cements are all packed and sterilized before delivery to the user.

The possibility of a successful bone ingrowth and bone ongrowth onto an implant surface can be considerably improved by covering the implant surface with the resorbable and injectable bone mineral substitute material composition according to the invention. When the implant during surgery is placed in the bone cavity the composition - which at this time is in a paste-like state - fills out the gaps between the bone and the implant and sets after the implant has been placed in the bone cavity. After surgery, the hardened bone mineral substitute material composition provides an additional stabilization of the implant. More importantly, improved conditions are obtained for bone ingrowth/ongrowth onto the implant, the long-term fixation as well as the length of life of the implant being increased. In this connection the conditions for bone ingrowth/ongrowth are further improved by the biologically active substance(s) in the bone mineral substitute material composition, such as bone morphogenetic proteins, vitamin E, or antibiotics.

CLAIMS

1. An injectable bone mineral substitute material composition comprising an inorganic bone cement powder and a biologically compatible oil, characterized in that the oil is a intermixture with the cement powder at a concentration of less than 10 wt% of the total weight of the composition in order to improve the rheology of the composition.

2. A composition as in claim 1, characterized in that a biologically active substance is dissolved, dispersed or emulsified in the biologically compatible oil to be released therefrom, after hardening of the composition to a bone mineral substitute, over a period of time.

3. A composition as in claim 2, characterized in that the biologically active substance is an antioxidant, a vitamin, a hormone, an antibiotic, a cytostatic, a bisphosphonate, a growth factor, or a protein, alone or in combination.

4. A composition as in claim 2 or 3, characterized in that the antioxidant and the biologically compatible oil is a vitamin E.

5. A composition as in claim 4, characterized in that the vitamin E is α-tocopherol.

6. A composition as in claim 3 characterized in that the hormone is oxytocin.

7. A composition as in claim 3, characterized in that the hormone is a growth hormone.

8. A composition as in any of claims 2-7, characterized in that the biologically active substance comprises 0.05-10 wt% of the hardened bone mineral substitute material.

9. A composition as in any of claims 1-3, characterized in that the biologically compatible oil is cotton seed oil, linseed oil, sunflower oil, olive

oil, soybean oil, maize oil, almond oil, peanut oil, palm oil, whale oil, or bone oil, alone or in combination.

10. A composition as in any of claims 1-9, c h a r a c t e r i z e d in that the cement powder is a calcium sulphate powder, a hydroxylapatite powder, or a calcium phosphate powder, alone or in combination.

11. A bone mineral substitute prepared from the composition as in any of claims 1-10, c h a r a c t e r i z e d in that it is hardened pellets, small beads, rods, or blocks.

12. A bone mineral substitute as in claim 11, c h a r a c t e r i z e d in that it is threaded on a string of a non-bioresorbable or bioresorbable material.

13. A bone mineral substitute as in claim 12, c h a r a c t e r i z e d in that the bioresorbable material is polylactide or polyglycol.

14. A method of intermixing a powder of an implant material and a biologically compatible oil to a composition, the oil comprising less than 10 wt% of the total weight of the composition, c h a r a c t e r i z e d in that the oil is mixed with the powder of implant material at a temperature between 30 °C and 120 °C.

15. A method as in claim 14, c h a r a c t e r i z e d in that the oil is mixed with the powder of implant material at a temperature between 50 °C and 90 °C.

16. A method as in claim 14 or 15, c h a r a c t e r i z e d in that the oil is mixed with the powder of implant material by means of rolling.

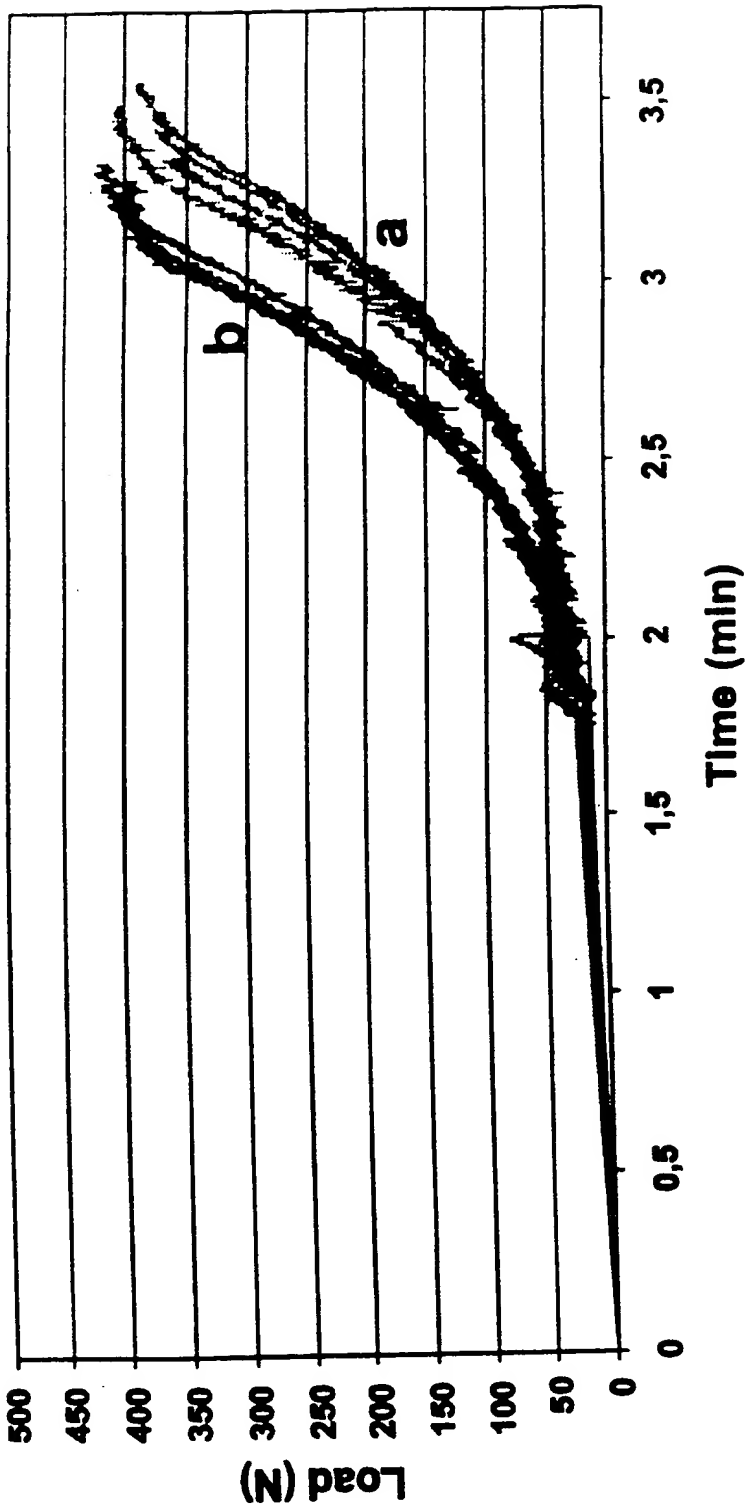
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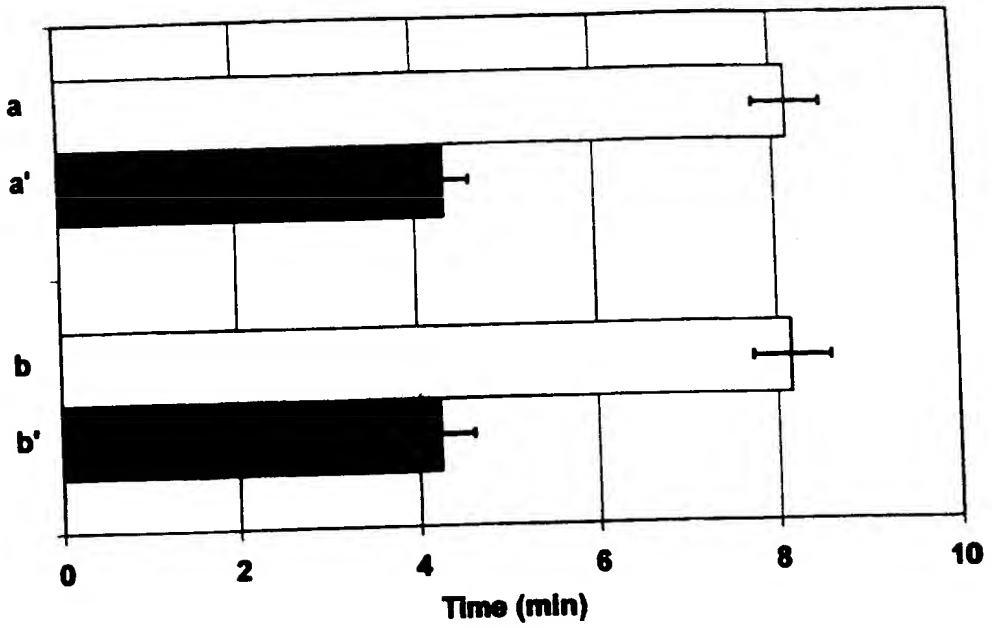
Fig 1

Fig 2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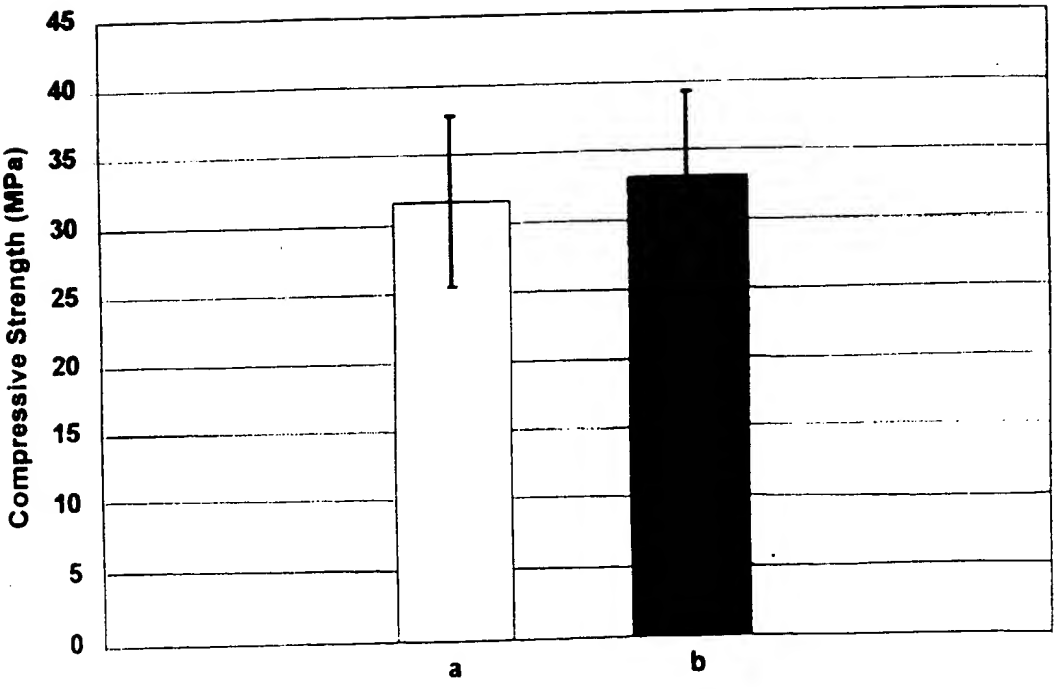
Time (min)

Fig 3


45
40
35
30
25
20
15
10
5
0
Compressive Strength (MPa)
a
b

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00789

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 24/02, A61L 24/04, A61L 27/54, A61L 27/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0045867 A1 (MATHYS ROBERT STIFTUNG), 10 August 2000 (10.08.00), claims 1-3,13,20,24 --	1-12
P,X	WO 0002597 A1 (GS DEVELOPMENT AB), 20 January 2000 (20.01.00), claims 1,12,17	1,2,7-10
P,A	--	3-6,11-12
A	SE 464912 B (BIOAPATITE AB), 1 July 1991 (01.07.91), claims, abstract --	1-12
A	EP 0109310 A2 (ETHICON INC.), 23 May 1984 (23.05.84), page 5, line 29 - page 6, line 21 --	1-12

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 July 2001	09 -07- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Ellen Setréus/Eö Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00789

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 9639202 A1 (OSTEOGENICS INC.), 12 December 1996 (12.12.96), page 11, line 6 - line 17, claims 1, 11,12,60, abstract	1-12
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A	EP 0495284 A1 (OSTEOTECH, INC.), 22 July 1992 (22.07.92), claims 1-12	1-12
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INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.
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